2. While the polypeptides share as a common structure a fibrinogen domain, the domains of NL-1, NL-5, and NL-8 are "only" 64-74% identical, and likewise the sequences of other regions of the ligands are different.

3. There is no indication that all ligands bind to the same TIE receptor.

Since the ligands were found to be distinct, antibodies specific to each ligand were also held distinct from one another, since they "would be expected to be structurally different in their variables [sic] regions and one specific antibody would not reasonably be expected to bind all ligands, specially in view of the sequence differences of the ligands." These reasons have formed the basis of separating inventions relating to each of the ligands.

Inventions I-III (nucleic acids) and IV-VI (polypeptides) were held "unrelated", since they are "structurally distinct and have different functions."

Inventions I-III (nucleic acids) and VII-IX (antibodies) were held "unrelated", since they are "structurally distinct", "cannot be used together and have different functions."

Inventions I-III (nucleic acids) were also found to be "unrelated" to the methods of inventions defined in Groups X-XII, XIII-XV, and XVI-XVIII, since "none of these methods can be used with a nucleic acid, but instead require an antibody or ligand." The Examiner further noted that "the methods cannot be used to produce a nucleic acid."

Inventions IV-VI (polypeptides) and VII-IX (antibodies) were held "unrelated", since the "ligand is structurally different from the antibody", and the "ligand and antibody have different functions."

With regard to inventions IV-VI and XVI-XIII (sic, probably XVI-XVIII) the Examiner noted that they relate to each other "as product and process of use." However, since "the ligand can be used in a materially different process such as in the production of a cognate antibody", the unity requirement is not met with regard to these groups either.

Inventions IV-VI were found to be unrelated to inventions XIII-XV, since the "ligands of Inventions IV-VI cannot be made by or used in the method of Inventions XIII-XV because that method requires the use [of] an antibody."

Inventions VII-IX were held "unrelated" to the methods of inventions X-VII and XVI-XVIII, since the antibodies of inventions VII-IX "cannot be used or made by the methods" specified in the method claims.

Inventions VII-IX and XIII-XV were characterized as "product and process of use", however, were held to be distinct since the antibodies of inventions VII-IX can be used "in a materially different process."

The method of inventions X-XII was held to be "unrelated" to the methods of inventions XIII-XV and XVI-XIII (sic, should be XVI-XVIII), since these methods "have different effects", and "different modes of operations."

The method of inventions XIII-XV were said to be "unrelated" to the method of inventions XVI-XIII (sic, should be XVI-XVIII), since these methods "have different modes of operation."

The Examiner concluded that since the foregoing inventions are distinct, "have acquired a separate status in the art as shown by their different classification", and "because of their recognized divergent subject matter (e.g. structurally and functionally distinct polypeptides or nucleic acids, methods with different effects or modes of operation), and the search required for each invention is not coextensive with another, restriction for examination purposes as indicated is proper."

As a result of the cancellation of claims 16-22, which was done without prejudice and without acquiescence in any part of the pending restriction requirement, the restriction requested with regard to Groups X-XVIII is now moot. The restriction/election requirement as it applies to the remaining claims (Groups I-IX) is vigorously traversed. For the event that the Examiner maintains the restriction requirement, the invention of Group IV is elected, with traverse.

II. *There should be no restriction between the inventions concerning NL-1, NL-5, and NL-8, respectively*

(1) Applicable law

35 U.S.C. § 121 states that the Commissioner may require restriction if two or more "independent and distinct" inventions are claimed in one application. Under 37 C.F.R. § 1.141, two or more "independent and distinct inventions" may not be claimed in one application. However, a finding that two or more inventions are separate and

distinct does not necessarily justify a restriction requirement. M.P.E.P. § 803 specifically states that

> *"There are two criteria for a proper requirement for restriction between patentably distinct inventions:*
>
> *(1) The inventions must be independent . . . or distinct as claimed . . .; and*
>
> *(2) There must be a serious burden on the examiner if restriction is not required. . ."*

(References to other M.P.E.P. sections omitted, emphasis added.)

Under the Guidelines provided in M.P.E.P. § 803, for a *prima facie* showing of a serious burden on the Examiner it is sufficient to show by appropriate explanation that the inventions have (1) a separate classification, or (2) acquired separate status in the art, or (3) a different field of research is required. This showing, however, is rebuttable by appropriate showings or evidence by the applicant.

Markush-type claims are provided special treatment by case law, and under the guidelines of the M.P.E.P. The criteria for restriction practice relating to Markush-type claims are set forth in M.P.E.P. § 803.02, which states:

> *"If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all claims on the merits, even though they*

are directed to independent and distinct inventions. In such as case, the examiner . . . will not require restriction.

(Emphasis added.)

Under the same section,

"unity of invention exists when compounds within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility."

However, even when a Markush-type claim includes independent and distinct inventions, the proper practice is not the issuance of a restriction requirement. Rather, the examiner *"may require a provisional election of a single species prior to examination on the merits."* (M.P.E.P. § 803.02). If on examination there is no prior art found that would anticipate the elected species, the search will be extended to the entire claim to determine its patentability.

According to M.P.E.P. § 803.04, the Commissioner has decided to partially waive the requirements of 37 C.F.R. § 1.141 *et seq.* with regard to nucleotide sequences, and permit a reasonable number of independent and distinct nucleotide sequences to be claimed in a single application. The referenced section further states that *"normally ten sequences constitute a reasonable number for examinations purposes. Accordingly, in most cases, up to ten (10) independent and distinct nucleotide sequences will be examined in a single application without restriction."* It is further provided that applicants may petition for examination of additional nucleotide sequences by

providing evidence that the different nucleotide sequences do not cover independent and distinct inventions.

(2) The examination of NL-1, NL-5, and NL-8 in one application does not place a serious burden on the Examiner

First, NL-1, NL-5, and NL-8 all are classified in class 435, subclass 69.1, i.e. do not have a separate classification.

Second, the Examiner's statement that these inventions have acquired separate status in the art "because of their recognized divergent subject matter (e.g. structurally and functionally distinct polypeptides or nucleic acids . . .)" is believed to be misplaced. The polypeptides of the present invention are structurally closely related, each containing a highly homologous fibrinogen domain. Specifically, the fibrinogen domain of NL1 is 74% identical with the fibrinogen domain of NL5 and 63% identical with the fibrinogen domain of NL8, while the fibrinogen domain of NL5 is 57% identical with the fibrinogen domain of NL8. (Page 56, first paragraph of the specification.) This high degree of sequence identity within a functional domain is convincing evidence of relatedness by any standards, and cannot be dismissed as insufficient without any further evidence. As the claims as currently amended contain no reference to biological activity, the alleged divergence in biological properties should no longer be a consideration.

Third, the examination of all nucleic acid, or all protein claims, or all claims concerning antibodies binding to the disclosed proteins, does not require a different field of research, since the proteins and their coding sequences are structurally closely related, and have the same classification for search purposes.

(3) Even if there was a burden on the Examiner, claims concerning NL-1, NL-5, and NL-8, respectively should be examined in a single application

Claim 1 (nucleic acid) and claim 8 (protein) are in Markush-type format. As the Markush group includes only four species, its members are "sufficiently few in number" so that under the guidelines of M.P.E.P. § 803.02all claims covering these species must be examined on the merits, regardless of the burden on the Examiner. Under the special provisions concerning Markush-type claims, even if the Examiner maintains that the individual proteins claimed are unrelated and diverse, the proper action would be a provisional election of species requirement, as discussed above.

(4) Nucleic acid sequences encoding NL-1, NL-5, and NL-8, respectively should be examined in a single application, regardless of their degree of relatedness

In M.P.E.P. § 803.04 the Commissioner provided for the examination in a single application, without restriction, of up to ten (10) "independent and distinct nucleotide sequences." During a telephone conference, the Examiner has represented that these provisions apply to EST sequences only, and were not intended to cover nucleotide sequences encoding polypeptides.

Nowhere in M.P.E.P. § 803.04 is there any reference to EST sequences. Nowhere is there any indication that the waiver effected by the Commissioner would not apply to all nucleotide sequences, regardless of whether they are hybridization probes, partial sequences which might or might not form part of a coding sequence, or full-length coding sequences. On the contrary, the plain language of the guidelines covers nucleotide sequences in general. Indeed, limiting this exception to EST sequences would lead to the absurd result that applicants who provide the public with

added valuable information (e.g., homology data, biological data, etc.) would be severely disadvantaged as compared to applicants whose only contribution to the general state of the art is the identification of a number of unrelated sequences of unknown function. Similarly, applicants would be disadvantaged merely for identifying nucleotide sequences as the coding sequences for a family of structurally and functionally related polypeptides. It is clear that such an unconscionable result could not have been intended by the Commissioner.

In view of the foregoing arguments, NL1, NL5, and NL8 should be treated as a single invention. A restriction requirement as to the nucleic acid molecules encoding these polypeptides, the polypeptides, and antibodies binding the polypeptides would be in accord with current practice of the Patent Office.

Applicants respectfully request the reconsideration and withdrawal of the pending restriction requirement, and the issuance of an early Office Action on the merits of the above-identified patent application.

Respectfully submitted,
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